Celecoxib, a Selective Cyclo-Oxygenase-2 Inhibitor, Enhances the Response to Preoperative Paclitaxel and Carboplatin in Early-Stage Non–Small-Cell Lung Cancer


Purpose: Preclinical studies suggest that treatment with a selective cyclo-oxygenase-2 (COX-2) inhibitor may augment the antitumor effects of chemotherapy. In this study, patients with non–small-cell lung cancer (NSCLC) were preoperatively treated with celecoxib in combination with chemotherapy. End points were toxicity, response rates, and measurement of intratumoral levels of prostaglandin E₂ (PGE₂).

Methods: In this phase II trial, 29 patients with stages IB to IIIA NSCLC were treated with two preoperative cycles of paclitaxel and carboplatin, as well as daily celecoxib, followed by surgical resection. Levels of PGE₂ in the primary tumors and adjacent normal lung tissue were compared in 17 study patients versus 13 controls, who received preoperative paclitaxel/carboplatin without celecoxib.

Results: All patients completed preoperative chemotherapy, and 26 completed preoperative celecoxib. The overall clinical response rate was 65% (48% with partial response; 17% with complete response). Grade 3 or 4 neutropenia was observed in 18 patients (62%). Twenty-eight patients were explored and underwent complete resection of their tumors. There were no complete pathologic responses, but seven patients (24%) had minimal residual microscopic disease. The addition of celecoxib to a regimen of paclitaxel and carboplatin abrogated the marked increase in levels of PGE₂ detected in primary tumors after treatment with paclitaxel and carboplatin alone.

Conclusion: In comparison with historically reported response rates, these data suggest that the addition of a selective COX-2 inhibitor may enhance the response to preoperative paclitaxel and carboplatin in patients with NSCLC. Moreover, treatment with celecoxib 400 mg twice daily was sufficient to normalize the increase in PGE₂ levels found in NSCLC patients after treatment with paclitaxel and carboplatin. Confirmatory trials are planned.


Non–Small-Cell Lung Cancer (NSCLC) is the leading cause of cancer deaths in the United States. Surgical resection, whenever possible, offers the best hope for cure. However, despite surgical resection, 5-year survival remains poor, even in patients with earlier stages of disease. For example, patients with clinical stages IB, II, and IIIA have a 5-year survival rate of only 15% to 40%.1 These poor results have stimulated interest in combined-modality treatment regimens, particularly chemotherapy followed by surgical resection. Although bimodality approach has generated encouraging results,2-4 the clinical and pathologic response rates after induction chemotherapy remain suboptimal. It is therefore necessary to evaluate novel treatment strategies that might improve the response to chemotherapy.

There is considerable evidence that cyclo-oxygenase-2 (COX-2), an inducible enzyme that catalyzes the synthesis of prostaglandins (PGs), represents a potential pharmacologic target for inhibiting tumor growth. Increased levels of COX-2 and PGs have been observed in a variety of malignancies, including NSCLC.5-8 Several mechanisms can potentially account for the tumor-promoting effects of COX-2–derived PGs. PGs can enhance tumor growth and metastasis by stimulating angiogenesis and invasiveness, in addition to inhibiting apoptosis and immune surveillance.9-21 Importantly, the formation and growth of tumors are reduced in mice engineered to be COX-2 deficient.10,22,23 Moreover, recently developed selective COX-2 inhibitors suppressed the formation, growth, and metastasis of tumors in experimental animals.11,21,22,24-36 In addition to its potential role in tumor promotion and progression, overexpression of COX-2 may also unfavorably alter the response of malignant cells to cytotoxic therapy. For example, we have previously shown that paclitaxel and other microtubule-interfering agents induce COX-2 and PG biosynthesis and have postulated that this might reduce the efficacy of paclitaxel.37 In theory, coadministration of a selective COX-2 inhibitor with paclitaxel would overcome any decrease in efficacy related to the induction of COX-2 by taxanes. This hypothesis is supported by preclinical evidence that selective inhibitors of COX-2 enhance the cytotoxic activity of both chemotherapy and radiotherapy in experimental models.38-42 Recently, Hida et al42 showed that addition of a selective COX-2 inhibitor augmented taxane-mediated inhibition of tumor growth in an experimental model of NSCLC.

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Despite these promising preclinical results, little is known about the antitumor effects of selective COX-2 inhibitors in humans. In one study, treatment with celecoxib, a selective COX-2 inhibitor, caused a reduction in the number of colorectal polyps in patients with familial adenomatous polyposis. The current study was designed to test the hypothesis that the addition of celecoxib would reduce the amounts of intratumoral prostaglandin E2 (PGE2) and improve the response rates associated with preoperative paclitaxel and carboplatin in patients with NSCLC. Furthermore, because of preclinical evidence that COX-2 can play a role in both wound healing and hematopoiesis, it was important to determine the safety of this preoperative regimen.

METHODS

From March 2000 through March 2002, 29 patients with histologically confirmed NSCLC were entered onto this phase II trial. Patients were considered eligible if they had potentially resectable disease and if their clinical stages were T2N0, T1/2N1, T3N0/1, or T1 to T3, N2. Pretreatment evaluation included a complete history and physical examination, routine laboratory evaluation, and chest computed tomography (CT). Positron emission tomography was added to the protocol after inclusion of the first three patients. Clinical T stage was determined by CT imaging, as well as bronchoscopy for T3 lesions. Nodal stage was determined by mediastinoscopy regardless of nodal size on CT scanning (n = 21) or by absence of activity in the mediastinum on positron emission tomography scanning (n = 8). Patients were considered ineligible for the study if they had received prior chemotherapy or radiotherapy, had unstable cardiovascular disease, or had a Karnofsky performance status of less than 80%. Because celecoxib is a sulfonamide, patients with a known or suspected allergy to sulfa drugs were excluded from participating. Adequate hematologic, renal, hepatic, and pulmonary function to undergo chemotherapy and the subsequent planned operation were mandatory. Additionally, all patients had to have a bidimensionally measurable target lesion. The protocol was reviewed and approved by the institutional review board, and informed consent was obtained from all patients. The consent form clearly described the investigational nature of the treatment plan, as well as the ability of the patient to withdraw consent at any time. Separate institutional review board approval was obtained to carry out PGE2 analyses on surgically resected lung tissues from patients who received preoperative paclitaxel and carboplatin. All tissues were snap frozen in liquid nitrogen and stored at −80°C until analysis.

Treatment Plan

Preoperative chemotherapy. Two cycles of paclitaxel and carboplatin were administered 21 days apart. Paclitaxel at 225 mg/m² was given as a 3-hour infusion, followed by a 1-hour intravenous infusion of carboplatin dosed to an area under the curve of 6 by the Calvert formula. All patients were premedicated with dexamethasone, diphenhydramine, and an H2 receptor antagonist.

Preoperative celecoxib. Celecoxib was given orally at a dose of 400 mg twice daily, starting on the first day of chemotherapy, until the morning of the surgical procedure. This dose was chosen because it was previously reported to cause a reduction in the number of colorectal adenomas in a recently completed trial. No dose escalation of celecoxib was allowed. Dose reductions or discontinuation of celecoxib were allowed if, in the judgment of the investigators, a particular toxicity was deemed likely to be due to celecoxib.

Response

A major objective response consisted of a complete clinical response or a partial response. A complete clinical response was considered present if there was no evidence of tumor on the restaging CT scan. A partial response was defined as at least a 50% reduction in the product of the perpendicular diameters of the primary tumor. Progression of disease was determined by an increase of 50% or more in the product of the perpendicular diameters of the index lesion or the appearance of new lesions. All other patients were considered to have stable disease.

Surgery

Patients without evidence of progression of disease underwent thoracotomy within 3 to 6 weeks after the second cycle of chemotherapy. Postchemotherapy evaluation included routine laboratory tests and a CT scan of the chest and upper abdomen. Restaging was performed 2 to 3 weeks after the second cycle of paclitaxel and carboplatin. Surgical resection required a lobectomy, sleeve lobectomy, or pneumonectomy. Segmentectomy and wedge resection were not allowed. All patients required a complete mediastinal node dissection (not sampling), including stations 2R, 4R, 7, 8, 9, and 10 for right-sided lesions and stations 5, 6, 7, 8, 9, and 10 for left-sided lesions.

Postoperative Therapy

Postoperative chemotherapy or radiotherapy was not mandated by the protocol, and further management was left to the discretion of the treating physician. Because the key end points of this study were feasibility, response rates, and PGE2 measurements, postoperative treatment with celecoxib was not a requirement of the study.

Analysis of PGE2

In study patients (treated with paclitaxel, carboplatin, and celecoxib) and control patients (treated with paclitaxel and carboplatin), specimens were obtained at the time of surgery from the primary tumor and the adjacent non-neoplastic lung at least 5 cm away from the tumor. There were 13 control patients who had received preoperative paclitaxel and carboplatin.

Levels of PGE2 were determined as in previous studies. In brief, frozen tissue was thawed in ice-cold buffer containing 150 mmol/L of NaCl, 100 mmol/L of Tris-buffered saline (pH 8), 1 mmol/L of EDTA, and 10 μmol/L of indomethacin (Sigma Chemical Co, St Louis, MO). Indomethacin, a dual inhibitor of COX-1 and COX-2, was added to prevent ex vivo synthesis of PGE2. After homogenization, tissues were sonicated twice for 20 seconds on ice and then centrifuged at 10,000 × g for 10 minutes at 4°C to remove particulate material. The protein concentration of the supernatant was measured using the Lowry protein assay kit (Sigma Chemical Co). Amounts of PGE2 in the supernatant were determined by enzyme immunoassay according to the manufacturer’s instructions (Cayman Chemical Co, Ann Arbor, MI). Levels of PGE2 were normalized to protein concentrations in the supernatant.

RESULTS

Twenty-nine patients were enrolled. Patients’ characteristics are listed in Table 1. Median age was 63 years, and the majority of patients were men. Pretreatment clinical stages were as follows: 16 patients had stage IIB disease, three patients had stage IIB disease, and 10 patients had stage IIIA disease.

Induction Therapy

All patients completed both cycles of paclitaxel and carboplatin preoperatively without any dose reductions. Celecoxib therapy was discontinued in three patients who had developed generalized allergic skin reactions 7 to 10 days after starting treatment with celecoxib. The remaining 26 patients completed celecoxib therapy without incident.

Response to Induction Therapy

Nineteen patients had a major clinical response. The overall clinical response rate was 65%. Five (17%) had a complete clinical response, and 14 (48%) had a partial response (Table 2). Among the three patients who discontinued celecoxib treatment,
two had a partial response and one had disease progression marked by an increase in the size of the primary tumor. In contrast, none of the patients who completed the treatment regimen containing celecoxib had progressive disease.

Surgical Treatment

One patient died as a result of neutropenic sepsis after the second cycle of chemotherapy. The remaining 28 patients underwent thoracotomy and resection. Lobectomy was performed in 17 patients, bilobectomy was performed in four patients, pneumonectomy was performed in six patients, and lobectomy with chest wall resection was performed in one patient. Postsurgical pathologic findings are listed in Table 3. No patient had a complete pathologic response. Seven patients (24%) had a significant response with only minimal residual microscopic disease detected in the resected specimen. Five of these patients had radiographic evidence of a complete response, whereas two had residual masses on CT scanning. Three of these patients had squamous cell carcinoma, three had adenocarcinoma, and one had a poorly differentiated tumor. Of the patients who did not complete celecoxib therapy, none had a significant pathologic response.

<table>
<thead>
<tr>
<th>Table 1. Patient Characteristics</th>
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<tbody>
<tr>
<td>No. of Patients</td>
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<td>Patients</td>
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<td>Age, years</td>
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<td>Male</td>
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<td>Female</td>
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<td>Clinical stage</td>
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<td>IB (T2N0)</td>
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<td>IIB (T2N1)</td>
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<td>IIB (T3N0)</td>
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<td>IIIA (T1/2N2)</td>
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<td>IIIA (T3N1/2)</td>
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<tr>
<td>Cell type</td>
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<tr>
<td>Adenocarcinoma</td>
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<td>Squamous cell carcinoma</td>
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<td>Large-cell carcinoma</td>
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<td>Poorly differentiated</td>
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<td>Karnofsky status</td>
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<td>80-90%</td>
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<td>100%</td>
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<th>Table 2. Response to Preoperative Therapy (n = 28)</th>
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<tr>
<td>Total</td>
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<td>IB (n = 16)</td>
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<td>IIB (n = 9)</td>
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<td>IIIA (n = 9)</td>
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<tr>
<td>Complete response</td>
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<td>Partial response</td>
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<td>Stable disease</td>
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<td>Progression</td>
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<td>No. of Patients</td>
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<th>Table 3. Postsurgical Staging (resection, n = 28)</th>
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<td>No. of Patients</td>
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<td>Stage IA</td>
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<td>Stage IB</td>
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<td>Stage IIA</td>
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<td>Stage IIB</td>
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<td>Stage IIIA</td>
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<td>Stage IIIB*</td>
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<td>Stage IV (T4)†</td>
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<td>Downstaged</td>
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<td>Upstaged</td>
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<td>Unchanged</td>
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*One patient had intralobar satellite lesions; one patient had N3 disease after mediastinal node dissection despite absence of N3 disease at mediastinoscopy.
†Multilobar satellite lesions.

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<th>Table 4. Induction Therapy Adverse Events</th>
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<td>Toxicity</td>
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<td>Grade 0</td>
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<tr>
<td>Allergy</td>
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<td>Hematologic toxicity</td>
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<td>Anemia</td>
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<td>Thrombocytopenia</td>
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<td>Granulocytopenia</td>
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<td>Infection</td>
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<td>Malaise/fatigue/lethargy</td>
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<td>Myalgia/arthralgia</td>
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<td>Nausea</td>
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<td>Vomiting</td>
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<td>Heartburn/dyspepsia†</td>
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<td>Neuropathy</td>
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<td>Numbness</td>
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<td>Parasthesia</td>
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<td>Phlebitis/thrombosis/embolism</td>
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*One patient died of neutropenic sepsis.
†Possibly celecoxib-related.

**Treatment-Related Toxicity**

There were two treatment-related deaths (6.8%). One patient died as a result of neutropenic sepsis before thoracotomy, and another patient died as a result of respiratory failure 1 week after a right pneumonectomy. Chemotherapy-related toxicity is listed in Table 4. Severe anemia occurred in only one patient. Grade 3 or 4 granulocytopenia occurred in 18 patients (62%), including one patient who died as a result of neutropenic sepsis. Grade 3 myalgia occurred in four patients. Peripheral neuropathy occurred in 14 patients and was grade 1 or grade 2 in all.

As mentioned above, three patients stopped taking celecoxib after developing a generalized skin rash. Eight of the remaining 26 patients who completed celecoxib therapy had grade 1 or grade 2 heartburn and/or dyspepsia. Gastrointestinal bleeding was not observed.

Surgical morbidity is listed in Table 5. There were no unexpected surgical complications. Despite concerns regarding the possible effects of COX-2 inhibitors on wound healing (mediated by inhibition of angiogenesis), there were no instances of impaired healing.
of impaired bronchial or wound healing. Chest tube drainage was maintained for a median of 4 days (range, 1 to 17 days), and median hospital stay was 5 days (range, 3 to 18 days).

Levels of \( \text{PGE}_2 \)

Tissue samples were available from 17 study patients (chemotherapy plus celecoxib) and 13 control patients. Tumor tissue was not available from seven study patients who had significant pathologic responses. Tissue was not obtained from one additional study patient. We compared levels of \( \text{PGE}_2 \) in resected tumors and nonneoplastic (nontumor) lung tissue from study patients and controls who received preoperative paclitaxel and carboplatin alone (Table 6). Mean levels of \( \text{PGE}_2 \) were increased more than 10-fold in the tumors (v nontumorous lung) of patients treated with paclitaxel and carboplatin only (Fig 1). This increase in amounts of intratumoral \( \text{PGE}_2 \) was observed regardless of cell type, stage, or clinical response. Remarkably, the addition of celecoxib to paclitaxel/carboplatin led to levels of intratumoral \( \text{PGE}_2 \) that were similar to levels in nonneoplastic lung (Fig 1, Table 6).

**DISCUSSION**

The hypothesis underlying the current study was that inhibiting COX-2 activity might enhance the response to cytotoxic agents through a number of mechanisms, including induction of apoptosis and inhibition of tumor-related angiogenesis.\(^9\)-\(^{16}\),\(^{47}\) The rationale was also based on our previous work, which showed that paclitaxel could induce COX-2 and PG biosynthesis,\(^{37}\) thus theoretically reducing its own cytotoxic effect. The study was thus designed to target the COX-2 enzyme by coadministering celecoxib with taxane-based chemotherapy in patients with NSCLC. The primary objective of targeted therapy is for the agent in question to hit its intended target. To our knowledge, this study provides the first evidence that the administration of celecoxib at 800 mg/d is sufficient to attenuate or abrogate intratumoral COX-2–derived \( \text{PGE}_2 \) biosynthesis, at least, in patients with NSCLC. In a previous study, this dose of

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<th>Table 5. Postoperative Morbidity</th>
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<td><strong>Toxicity</strong></td>
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<td>Arrhythmia</td>
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<td>Respiratory failure</td>
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<td>Pneumonia</td>
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<td>Wound infection</td>
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<td>Prolonged air leak (( &gt; 7 ) days)</td>
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*Operative mortality.

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<th>Table 6. Celecoxib Reduces Amounts of ( \text{PGE}_2 ) in Non–Small-Cell Lung Cancer</th>
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<td><strong>Group</strong></td>
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Abbreviation: \( \text{PGE}_2 \), prostaglandin \( \text{E}_2 \).
celecoxib was found to reduce colorectal polyp burden in familial adenomatous polyposis patients, but the effects on PG levels were not reported. Moreover, this dose of celecoxib is being used in numerous other clinical trials that are under way. Whether lower doses of celecoxib will be sufficient to maximally inhibit COX-2 activity is unknown.

The data included in this report allow us to make several additional observations. The addition of celecoxib to the regimen of paclitaxel and carboplatin seems to be feasible and safe. Overall treatment-related toxicity and mortality were acceptable. However, we observed a higher incidence of neutropenia than that ordinarily anticipated after paclitaxel and carboplatin therapy alone. Pisters et al reported grade 3 or 4 neutropenia in 35% of patients in the Bimodality Lung Oncology Team (BLOT) trial, compared with 62% in the present study. At least one preclinical study suggested that COX-2 might play a role in the recovery phase of chemotherapy-induced bone marrow injury. Although we are unable to determine the precise duration of bone marrow injury, neither dose reduction nor dose delay occurred as a consequence of neutropenia. We had previously suggested that concomitant administration of celecoxib may reduce the incidence or severity of taxane-associated myalgia and arthralgia. Because only a few patients experienced grade 3 myalgia or arthralgia in this study, we are unable to substantiate or refute the efficacy of celecoxib in this regard. Finally, our initial concerns regarding the potential impact of COX-2 inhibition on wound healing were not realized. The overall postoperative mortality and morbidity were 4% and 28%, respectively. Although the overall clinical response rates were nearly comparable to those previously reported, we are encouraged by what seems to be an improvement in the proportion of patients (17%) who achieved a complete clinical response. This rate of clinical response is potentially significant, because 34% of our patients had stage IIIB disease, compared to only 7% in the BLOT report. Clinical response notwithstanding, none of our patients had a complete pathologic response. However, seven patients had a substantial pathologic response with only minimal residual microscopic disease detected on histologic examination. The clinical significance of this finding is uncertain at present. Additional studies are necessary to determine whether combining celecoxib with taxane-based chemotherapy will be of clinical benefit.

REFERENCES


